label thus detected to the group to which said label is bound, thereby simultaneously obtaining values individually representative of the levels of thyroid stimulating hormone, triiodothyronine, thyroxine, and anti-thyroid peroxidase.

REMARKS

The changes made by this amendment are matters of form and clarity that were inherent in the original claim language and do not concern matters of patentability. No new matter is presented by this amendment.

Claim Rejections – 35 USC § 112

The functional relationship between the particle coatings and the biological markers indicative of thyroid disorders is clarified by the explicit recitation of the markers in the preamble. Although explicit mention is not strictly necessary since these four species are recognized in the art as the biological markers for thyroid disorders, the insertion of these species in explicit terms has been made to further the examination of these claims. The relationship between the particle coatings and the various markers is simply that particles coated with anti-thyroid stimulating hormone (anti-TSH) will bind to thyroid stimulating hormone (TSH) in the sample, particles coated with anti-triiodothyronine (anti-T3) will bind to triiodothyronine (T3) in the sample, particles coated with anti-thyroxine (anti-T4) will bind to thyroxine (T4) in the sample, and particles coated with either thyroid peroxidase (TPO) or anti-human IgG will bind to anti-thyroid peroxidase (anti-TPO) in the sample. Due to the nature of antibodies, each individual particle coating will bind to its designated analyte and not to the others. (Anti-human IgG will bind to all human IgG but only anti-TPO will ultimately be detected because the step (b) of the claim recites the binding of the resulting complex with labeled TPO.) There is no "gap" between the necessary structural connections; "structural cooperative relationships of elements" are clearly set forth.

The examiner has expressed difficulty in understanding how the four groups are distinguishable from each other by flow cytometry as recited in claim 1. The

particular characteristic of the particles that enables them to be distinguished from each other by flow cytometry is not part of the invention in claim 1. The prior art contains many ways of distinguishing different groups of particles by flow cytometry, and any one of these ways can be used in the practice of this invention. The only limitation is that some means for distinguishing the groups be present, and this is what the claim recites (see the line immediately preceding subparagraph (b) of claim 1). The specification gives numerous examples of differentiation parameters (i.e., means of distinguishing the groups) in the paragraphs extending from page 14, line 21 through page 17, line 4. With this supporting description, there is no lack of definiteness in the scope of the claim in this regard.

The preamble has been amended as suggested by the examiner.

An objection has been raised to the word "composition" in the phrase "a labeled analog composition." The meaning and scope of this entire term, including the word "composition," is provided in the specification at page 10 in the paragraph beginning on line 21, with specific examples shown on the succeeding pages. As noted in the paragraph, the composition can include one species or more than one, and its only limitations are those recited in claim 1, i.e., it is fully characterized by its functional description in the claim.

The recitation of "group (v)" in step (b)(3) of claim 1 was an inadvertent error and has been corrected.

The examiner has expressed a lack of understanding of how the label becomes bound to the particles, in reference to step (c) of claim 1. The explanation is that this occurs by conventional immunochemistry through either sandwich-type binding or sequential competitive binding, with the labels becoming bound as a necessary consequence of the sequential incubations of steps (a) and (b). If analyte TSH is present in the sample, it will bind to the anti-TSH coating on the appropriate particle, and the labeled anti-TSH will then bind to the particle through the coating and the analyte. A similar binding sequence occurs with anti-TPO. If the analytes T3 or T4 are present in the sample, they will bind to their respective particles through the anti-T3 and anti-T4

coatings, respectively, on those particles, and any anti-T3 and anti-T4 left over on the particles will then bind to the labeled analog composition. In all of these sequences, the labeled species becomes bound to the particle either through the coating and analyte or the coating along (in competition with the analyte). This is adequately explained in the specification as well as being common knowledge among those skilled in the art.

The phrase "thus recovered" in step (c) of claim 1 has been clarified by inserting the qualifying phrase "from said second suspension."

The examiner also states that claim 1 fails to recite how "differential detection" (the examiner's words) of TSH, T3, T4, and anti-TPO is achieved, and that the particles as recited are distinguishable only by virtue of the binding member that is immobilized to each particle. The claim as originally drafted contained the limitation that the groups were distinguishable from each other by flow cytometry, wording that was intended to indicate that the groups had some distinguishing characteristic that enabled them to be distinguishable by flow cytometry, whether or not this characteristic was the binding member coatings themselves. The claim has now been reworded to emphasize that it is a characteristic of the particles other than the coatings listed in subparagraphs (i), (ii), (iii), and (iv) that makes the groups distinguishable by flow cytometry. The characteristic that allows this distinction to be made is thus not the binding members that are bound to the particles, but instead conventional flow cytometry distinguishing features, such as particle size, light scatter, light emission, fluorescence, absorbance, etc., all controllable independently of the binding member to which the analytes become bound during the assay. These distinguishing parameters are all explained in the specification at page 14, line 21 through page 16, line 24, and each is known in the art. As explained above, the invention is not limited to any particular differentiation parameter; it simply requires that at least one be present so that the groups, and hence the individual assays for each analyte, can be differentiated from each other by means other than the assay being performed by each group of particles.

The rejection of claims 2-22 as having improper antecedent basis is incorrect. Each of these claims is a method claim dependent on another method claim,

each ultimately dependent on claim 1. There is no inconsistency or lack of antecedent basis in the phrase "A method according to claim ..."

The rejection of claim 3 is traversed for the same reasons given above. With the amendment to claim 1 and the explanation offered above, it is now clear that the various particle groups are distinguishable from each other by flow cytometry, and this distinction is not the binding members that are bound to the particles, but instead conventional flow cytometry distinguishing features as set forth in the specification. Nor are the "labels" the distinction. The labels merely permit the assays to detect whether binding has occurred. The labels do not have to be differentiable among themselves, since once the particle groups are distinguishable by the conventional flow cytometry parameters such as particle size, fluorescence, light scattering, etc, the labels for each group are readily determined and correlated with the group distinctions to provide an analytical result for each group independently of the others.

The rejection of claim 4 is also traversed for the same reason. It is not the label that differentiates T3 from T4. Instead, it is the particle group and its flow cytometry distinguishing parameter that performs the differentiation. This parameter is independent of the label that indicates whether binding has occurred.

The rejection of claim 11 is likewise traversed, although the phrase being objected to ("common label") does not appear in claim 11 but rather in claim 10. Differential detection is achieved as explained in the paragraph above.

The rejection of claim 12 is traversed, since each of the features objected to is fully explained in the specification. The means by which dyes are incorporated into the particles is explained in the specification at page 16, line 31 through page 17, line 14, including examples of particles that are commercially available with dyes already incorporated in them. The dyes serving as differentiation parameters (in those embodiments of the invention where the differentiation parameter is indeed a dye or a combination of dyes) are not related to the labels used for assay detection; the two operate independently of each other. An explanation of how this is done appears on page 15 in the paragraph on lines 17 through 26. One method, as explained in the paragraph,

is the use of fluorescent materials with different emission spectra, such as fluorescein at different concentrations for the differentiation parameter distinguishing the particle groups by flow cytometry, and phycoerythrin as the assay detection dye. The two are detectable independently of each other, thereby allowing them to serve independent functions. This is only one example, but it illustrates how dyes can be used as both a flow cytometry differentiation parameter and a label for each assay.

In claim 12, the labels become bound to the particles by the immunological binding through the analyte. This is the common and well-known sandwich-assay-type binding and is fully explained throughout the specification and well understood among those skilled in immunology and immunoassays. The presence of bound labels indicates the presence of the analyte in the sample.

In claims 20, 21, and 22, the difference in particle size (claim 20), coating density of anti-TSH (claim 21), and both particle size and coating density of anti-TSH (claim 22) between the two particle subgroups allows the larger-size or higher-density particles to bind more analyte than they would if they were smaller or lower-density particles. Assuming two analytes, each with its own particle subgroup bearing the appropriate binding member for that analyte, if both particle subgroups had particles of the same size and coating density and one analyte is in a significantly lower concentration range than the other, then the sensitivity of the assay for that analyte would be lower because less of the analyte would bind to the particles. According to claim 20, the sensitivity for that analyte is increased by using a larger particle size for that analyte's particle group than for the other analyte's particle group. More of the low concentration analyte would then bind to its respective particles since the particles have more available binding surface due to their larger size. This is how the particle size relates to the sensitivity. Likewise for claim 21, where instead of particle size, the difference is in the coating density of the binding member, i.e., more of the low concentration analyte would bind to its respective particles since the particles have more binding members per particle.

The term "useful" in these claims does not lack a comparative basis. It simply means that with the greater sensitivity obtained by the use of different particle sizes, different coating densities, or both, the analyte that is present in a low concentration, i.e., TSH which is often present in lower concentrations than the other three biological markers and more difficult to quantify, can be measured just as easily as the particles whose concentrations lie within a higher range. Claim 20 states that the difference in particle size is sufficient to improve the sensitivity of the assay for TSH without simultaneously affecting the sensitivity of the assay for the other analytes. Likewise, claim 21 states that the difference in coating density is sufficient to improve the sensitivity, and claim 22 states that the combination of the differences in size and coating density are sufficient to improve the density.

The term "the other" in these claims refers to the other subgroup, i.e., the subgroup other than the one the provides the greater sensitivity. Read in context, the meaning is clear: "such that one subgroup provides a substantially greater sensitivity ... than the other."

For the reasons set forth above, all rejections under 35 USC § 112 are respectfully traversed, and reconsideration is respectfully requested.

Claim Rejections – 35 USC § 103

Each of the rejections under 35 USC § 103 cites as its primary reference the U.S. Patent No. 6,280,618 to Watson et al. The use of the '618 patent is improperly cited as a reference in view of 35 USC § 103, subparagraph (c), which states:

> (c) Subject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

The '618 patent qualifies as prior art only under subsection (e) of section 102 since its issue date postdates the filing date of the present application, it names different inventors,

the portion cited in the rejection is subject matter that the patent discloses but does not claim, and the two are commonly owned by Bio-Rad Laboratories, Inc. The ownership of the '618 patent is indicated on its cover sheet, and that of the present application is established by the assignment recorded at the United States Patent and Trademark Office on December 19, 2000, on Reel/Frame 011403/0562, which likewise indicates Bio-Rad Laboratories, Inc. Therefore, all rejections relying on the '618 patent are traversed for this reason.

Aside from the lack of status of the '618 patent as prior art, other rejections under 35 USC § 103 in the Office Action are without foundation. While the allowability of claim 6 is noted with appreciation, Applicants respectfully submit that the rejection of claims 4 and 5 is without merit. The rejection cites the Evans et al. patent (US 5,071,773) for its disclosure of competition binding of T3 with 3,5',3'-triiodo-L-thyronine. Although the location of this disclosure in Evans et al. is not given, Applicants believe that the examiner is referring to the section in column 48 under the heading "III.E. Thyroid Hormone Binding." This is a disclosure of the use of the ^{125}I analog of 3,5',3'-triiodo-L-thyronine in a competitive hormone binding assay where it competes with 3,5',3'-triiodothyroacetic acid and other compounds including T3 itself for binding to the native thyroid hormone receptor. This has nothing to do with the subject matter of Applicants' claims 4 or 5. The closest compound recited in these claims is labeled N-*tert*-butyloxycarbonyl-3,5',3'-triiodo-L-thyronine, which is structurally far removed from 3,5',3'-triiodo-L-thyronine or its ^{125}I analog. Furthermore, Applicants' invention in these claims does not involve binding to a hormone receptor; it addresses the binding of labeled analogs to antibodies of T3 and T4. Specifically, these claims recite the use of labeled analogs as a common binding reagent that binds to both anti-T3 and anti-T4 at the same time in a common assay for both. The Evans et al. disclosure says nothing about the use of antibodies, much less the use of an antibody to T4 and the binding of a common labeled species to both antibodies in a sequential competitive assay for both at the same time. Accordingly, there is no suggestion of the invention in either of claims 4 or 5 in the disclosure of Evans et al., either alone or combined with the other

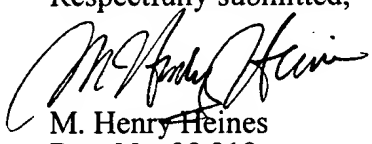
references with which Evans et al. is cited. The rejection of claims 4-5 is therefore respectfully traversed for this reason in addition to the reason stated in the preceding paragraph.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (amended) A method for analyzing a single patient sample to simultaneously determine levels of **thyroid stimulating hormone, triiodothyronine, thyroxine, and thyroid peroxidase, as a collective indication** [indicative] of thyroid disorders, said method comprising:

(a) incubating said sample with a mixture of particles in a first suspension, said mixture of particles comprised of groups (i) through (iv):

(i) particles coated with anti-thyroid stimulating hormone,

(ii) particles coated with anti-triiodothyronine,

(iii) particles coated with anti-thyroxine, and

(iv) particles coated with a mixture of a diluting agent and a member selected from the group consisting of thyroid peroxidase and anti-human IgG,

the particles of each group distinguishable from **the particles of** each other group by **a** flow cytometry **distinguishable characteristic that is independent of the coatings of subparagraphs (i), (ii), (iii), and (iv)**;

(b) recovering said particles from said first suspension, and incubating said recovered particles with a mixture of labeled binding members in a second suspension, said mixture of labeled binding members comprising:

(1) labeled anti-thyroid stimulating hormone,

(2) a labeled analog composition toward which anti-triiodothyronine and anti-thyroxine have immunological binding affinity, but in which said immunological binding affinity is less than that of

anti-triiodothyronine toward triiodothyronine and of anti-thyroxine toward thyroxine, and

(3) either labeled anti-human IgG when particles of group (iv) are coated with thyroid peroxidase, or labeled thyroid peroxidase when particles of group **(iv)** [(v)]are coated with anti-human IgG;

said diluting agent being inert toward said biological markers and said labeled binding members; and

(c) recovering said particles from said second suspension and detecting the amount of label bound to said particles thus recovered **from said second suspension** while correlating by flow cytometry the amount of label thus detected to the group to which said label is bound, thereby simultaneously obtaining values individually representative of the levels of thyroid stimulating hormone, triiodothyronine, thyroxine, and anti-thyroid peroxidase.